REMARKS

Claims 1-3, 18 and 19 are pending in the application. Applicants have herewith cancelled claims 4-17, without prejudice or disclaimer, as being drawn to non-elected subject matter. Applicants reserve the right to prosecute these claims in successive divisional or continuation applications. Claims 1 and 2 have been amended and new claims 18 and 19 have been added. Support for the amendment to claim 1 can be found at, *e.g.*, page 8, lines 12-15; and page 12, lines 15-16. Support for the new claims can be found at, *e.g.*, page 8, lines 12-15. No new matter has been added.

Sequence listing

The Examiner has indicated that the application fails to comply with 37 CFR §§ 1.821-1.825. Applicants have filed herewith an initial paper copy of the sequence listing, an initial CRF, and a Statement in Support of the CRF.

Rejections under 35 U.S.C. § 112, first paragraph

Written description

Claims 1-3 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner has stated that the present invention "includes pharmaceutical formulations comprising such peroxiredoxin variants and functional analogs, carrying modifications like substitutions, deletions, insertions, inversions or cyclisations." (See Office action, page 2).

Applicants have herein amended claim 1 to specify that the claimed peroxiredoxin is a naturally occurring peroxiredoxin selected from the group consisting of peroxiredoxins I-VI. Claim 2 requires that the naturally occurring peroxiredoxin is either a type I peroxiredoxin or a type II peroxiredoxin. New claims 18 and 19 require that the naturally occurring peroxiredoxin is either NKEF-A or NKEF-B, respectively.

Naturally occurring peroxiredoxins are disclosed by the as-filed specification. Specifically, the specification describes peroxiredoxin subfamilies I-VI and indicates that the claimed peroxiredoxin family member can be from a mammalian source, such as humans, mice, rats, or cows, or a non-mammalian source, such as bacteria. (*See*, *e.g.*, page 7, line 8 to page 8,

line 4; 8, lines 9-22; page 11, line 27 to page 12, line 14; and page 14, lines 4-7). Moreover, multiple species of peroxiredoxin subfamilies are also provided by the specification. For example, the specification discloses human peroxiredoxins NKEF-A (a peroxiredoxin I), NKEF-B (a peroxiredoxin II), thiol-specific antioxidant (a peroxiredoxin II), Proliferation-associated protein (Pag; a peroxiredoxin I), human MER5 (a peroxiredoxin III), and human ORF6 (a peroxiredoxin VI). (*See, e.g.*, page 12, lines 1-14). Thus, because the specification describes a representative number of species of naturally occurring peroxiredoxins, Applicants contend that the specification adequately describes the genus including peroxiredoxins I-VI.

Likewise, Applicants have also disclosed structural requirements for the functional activity of the claimed peroxiredoxins (*e.g.,* naturally-occurring peroxiredoxins I-VI). (*See, e.g.*, page 14, lines 4-7). Specifically, Applicants have demonstrated specific N-terminal and C-terminal cysteine-containing domains that are associated with the redox activity of the peroxiredoxin polypeptides. As noted in the specification, specific peroxiredoxin subfamilies require 2 cysteines (2-Cys peroxiredoxins (peroxiredoxins I-V)) while another peroxiredoxin subfamily requires only 1 cysteine (1-Cys peroxiredoxins (peroxiredoxin VI)). (*See, e.g.*, page 8, lines 9-16; and page 14, lines 4-7). Therefore, contrary to the Examiner's contention, Applicants have sufficiently described the claimed naturally occurring peroxiredoxins (selected from the group consisting of peroxiredoxins I-VI), in terms of both function and correlated structure.

For all of these reasons, Applicants contend that the claimed subject matter is sufficiently described in the specification so as to convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Thus, the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, for lack of written description should be withdrawn.

Enablement

Claims 1-3 have also been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner has stated that as used in the pending claims the term peroxiredoxin encompasses a broad genus of allelic variants, species variants, conservative amino acid substitution variants, fragments, substitutions, deletions, insertions, inversions or cyclisations. (See Office action, pages 6, 8). The Examiner further states that the disclosure fails to provide any guidance pertaining to the molecular determinants that modulate peroxiredoxin anti-viral activity, and that the disclosure does not reasonably suggest which peroxiredoxin allelic variants,

species variants, conservative amino acid substitution variants, fragments, substitutions, deletions, insertions, inversions or cyclisations have anti-viral activity. (See Office action, page 7). Moreover, the Examiner also asserts that the disclosure fails to provide any working embodiments and that the state of the art of HIV-1 antiviral development is unpredictable. Thus, the Examiner concludes that it would require undue experimentation for one of ordinary skill in the art to practice the claimed invention. Applicants traverse these assertions to the extent they apply to the pending claims, as amended herein.

1. The as-filed specification discloses structural requirements necessary for the functional activity of the claimed peroxiredoxins.

The Examiner has indicated that the skilled artisan would require a knowledge of those regions of a given peroxiredoxin that are *sine qua non* for the inhibitory activities of the peroxiredoxin protein. (See Office action, page 7). As noted above, Applicants have herein amended claim 1 to specify that the claimed peroxiredoxin is a naturally occurring peroxiredoxin selected from the group consisting of peroxiredoxins I-VI. In fact, the specification discloses that specific N-terminal and C-terminal cysteine-containing domains control the redox activity of peroxiredoxin polypeptides (*See, e.g.*, page 8, lines 9-16). Applicants enclose herewith as Appendix A, a CLUSTALW alignment of several peroxiredoxins, including NKEF-B (a peroxiredoxin II), TSA (a peroxiredoxin II), Pag (a peroxiredoxin I), MER5 (a peroxiredoxin III), and anti-oxidant enzyme AOE372 (a peroxiredoxin IV), which demonstrates the conservation of these cysteine-containing domains, as disclosed in the specification.

Moreover, the specification also discloses that the redox activity of peroxiredoxins is important in the function of these proteins to counterbalance the toxic effects of reactive oxygen species (ROS), effects which include protein modification, DNA base modification, DNA strand breaks and lipid peroxidation, as well as modulate the impact of ROS signaling on cell proliferation and differentiation, immune response, and apoptosis. (*See, e.g.*, page 8, lines 22-26). ROS imbalance has also been shown to be associated with HIV activation. (*See, e.g.*, page 9, lines 4-7).

Therefore, Applicants assert that the as-filed specification does define those regions of a given peroxiredoxin that contribute to the anti-HIV activities of the claimed peroxiredoxin proteins.

2. The specification discloses that the claimed peroxiredoxins display the requisite anti-viral activity required for the treatment of HIV-1 infection.

The Examiner has indicated that the disclosure fails to identify those portions of NKEF-A and –B that are required for antiviral activity and whether these regions are present in other peroxiredoxin family members. (See Office action, page 7). As noted above, the specification describes the specific N-terminal and C-terminal cysteine-containing domains that control the redox activity of peroxiredoxin polypeptides. (*See, e.g.*, page 14, lines 4-7). Moreover, as demonstrated in Appendix A, these regions are conserved in several related peroxiredoxin polypeptides, including members of the peroxiredoxin I-IV subfamilies.

The Examiner also states that "the disclosure fails to detail the preparation of a single variant with the desired activity." (Office action, page 7). Applicants note that the pending claims have been amended herein to require naturally occurring peroxiredoxins. Thus, variants are not encompassed by amended claim 1. As detailed above, the specification describes a genus of naturally occurring peroxiredoxin polypeptides that function to inhibit infection of cells by HIV-1, including peroxiredoxins I-VI.

Therefore, based on the teachings of the specification, Applicants contend that the skilled artisan would be able to identify functioning members of the peroxiredoxin family without undue experimentation.

3. The pending claims are drawn to a defined genus of naturally occurring peroxiredoxin polypeptides having the claimed anti-viral activity.

The Examiner has also indicated that the disclosure fails to provide sufficient guidance regarding the structural regions modulating peroxiredoxin anti-viral activity, regarding which family members share these regions, and regarding which portions of the protein can be modified in such a manner as to provide therapeutic activities. (See Office action, page 8). Applicants disagree.

The specification discloses (by accession number) many peroxiredoxins having the cysteine-containing domains important to peroxiredoxin redox activity. (*See, e.g.*, page 7, line 8 to page 8, line 4; 8, lines 9-22; page 11, line 27 to page 12, line 14; and page 14, lines 4-7). Moreover, the specification also defines these cysteine domains, which as noted above, are critical to the anti-viral functions of these polypeptides. (*See, e.g.*, page 14, lines 4-7). Further,

the specification discloses the anti-viral activities of a representative number of peroxiredoxins, including NKEF-A (a peroxiredoxin I), and NKEF-B (a peroxiredoxin II). Since the pending claims are drawn to naturally occurring peroxiredoxin polypeptides, proposed artificial modifications (*e.g.*, variants, fragments, deletions, etc.) to the peroxiredoxin polypeptide would fall outside the scope of the currently amended claims. Therefore, contrary to the Examiner's contention, the instant claims are not directed to a large genus of compounds. Rather, the claims, as amended, recite naturally occurring peroxiredoxins having anti-viral activity.

4. The specification provides working embodiments of peroxiredoxins having anti-viral activity.

The Examiner has indicated that the specification fails to provide any working embodiments, stating that while the specification demonstrated that "NKEF-A and NKEF-B displayed *in vitro* inhibitory activities, such simple tissue culture models are not generally considered to be predictive of clinical accuracy." (Office action at page 8).

As amended herein, the pending claims are directed to methods of treating HIV-1 infection by contacting a cell susceptible to HIV-1 infection with an effective amount of a naturally occurring peroxiredoxin I-VI sufficient to inhibit infection of the cell by HIV-1. In the instant specification, Applicants have demonstrated that two naturally occuring peroxiredoxins, NKEF-A (a peroxiredoxin I), and NKEF-B (a peroxiredoxin II), suppress HIV infection when contacted with human T lymphoblast cells infected with HIV. (*See*, *e.g.*, Figure 2). Applicants have also demonstrated that cells transfected with NKEF-A or NKEF-B are protected against HIV-1 infection. (*See*, *e.g.*, Figures 5 and 6).

Moreover, a subset of the *in vitro* tests disclosed in the specification, which demonstrate inhibition of HIV-1 replication by NKEF-A and NKEF-B, are performed by measuring the reduction in the amount of the p24 antigen following addition of NKEF-A or NKEF-B. (*See*, *e.g.*, Figure 2). This assay is identical to the viral p24 antigen ELISA described on page 52 of Patience et al., Mol. Biotech 1994, 1:49-58 ("Patience"), a reference provided by the Examiner in the pending Office action. As indicated by Patience, the p24 assay systems used to measure various stages of the HIV life cycle are very convenient for assessing the antiviral activity of compounds. (*See*, Patience, page 49). Thus, Applicants assert that the p24 ELISA assay disclosed in the specification is an art-recognized method of demonstrating viral inhibition by a compound of interest.

The Examiner also indicates that the evidence disclosed in the instant application that NKEF-A and NKEF-B are elevated in a subset of non-progressing HIV-positive patients, as demonstrated in Figure 3, is not predictive of clinical success. According to the Examiner, these elevated results are not observed in a majority of patients. Moreover, the Examiner suggests, without providing any evidence, that those non-progressing patients with elevated NKEF-A and NKEF-B may have been infected with an effete virus or may have a robust immune response. Applicants disagree.

The non-progressing patients having elevated NKEF-A and NKEF-B had levels that were as high as 500ng/ml for NKEF-A and NKEF-B (*See, e.g.,* Figure 3), resulting in a total NKEF concentration of about 1μg/ml, a concentration of NKEF at which inhibition of HIV infection has been disclosed. (*See, e.g.*, Figure 2 and page 36, lines 11-20).

Thus, Applicants contend that these results demonstrate the efficacy of peroxiredoxins to inhibit infection of cells by HIV-1.

5. The art of HIV-1 anti-viral development is not unpredictable.

The Examiner has indicated that several factors, including the incomplete determination of the pharmacological profile of a peroxiredoxin, the incidence of drug-resistance of HIV infection, the large quantities of virus present in the hematopoietic and lymphatic compartments, and the lack of adequate animal models, make the assessment of antiviral effectiveness unpredictable. Moreover, the Examiner further indicates that the specification fails to address any of these caveats. Thus, the Examiner concludes that it would require undue experimentation to practice the claimed invention. Applicants traverse.

The specification describes the use of art-recognized *in vitro* models useful to measure HIV infection in cell culture and the effect of target therapeutics. For example the specification demonstrates that the inhibition of HIV replication expressing the NKEFs is quantitated by measuring the concentration of the p24 antigen using ELISA. (*See, e.g.*, page 37, line 21 to page 38, line 3). Patience discloses that the p24 ELISA assay is a useful method to identify compounds with antiviral activity. (*See,* Patience, page 52).

The instant specification describes the *in vivo* introduction of peroxiredoxin into mice bearing human cells, cultivated in hollow fibers within the subcutaneous and intraperitoneal compartments of the mice. (*See, e.g.*, page 38, line 14, to page 39, line 5). This system allows

for the pharmacological profile of peroxiredoxins to be ascertained, and it addresses the lack of standard *in vivo* animal models endorsed by the US FDA. (*See, e.g.*, page 38, lines 14-16). The ability to target a certain organ or tissue is also described in the specification, which teaches the targeting of genes encoding peroxiredoxins to specific cells or tissues using inducible regulatory elements. (*See, e.g.*, page 38, lines 3-6).

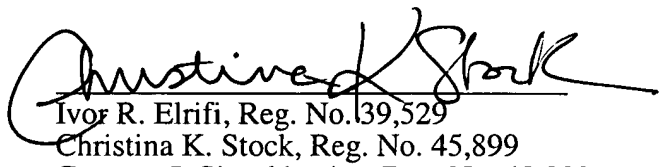
For these reasons, Applicants contend that one skilled in the art with the specification in hand in connection with the level of knowledge possessed by those of ordinary skill in the art, could practice the invention as claimed without undue experimentation. Thus, this rejection can be withdrawn.

CONCLUSION

Applicants submit that the claims as here amended put the application in condition for allowance, and such action is respectfully requested.

Should any questions or issues arise concerning the application, the Examiner is invited and encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



August 12, 2004

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